Remarks

This amendment is supplemental to the amendments filed on June 11, 2007 and on July 16, 2007 and adds two new claims, claims 39 and 40. The claims have been added at this time in view of the new continuation rules scheduled to go into effect November 1, 2007. No new matter is added.

In new claim 39, the medicament compound that can be used in place of cyclopamine is described as "or another compound that specifically inhibits Hedgehog/Srnoothened signaling." This description of a compound that can be used in the described method of treatment in place of cyclopamine contributes to the clarity and certainty of claim. Extensive support exists in the specification for claim 39.

Cyclopamine (11-deoxojervine) and other teratogenic *Veratrum* alkaloids (e.g. jervine) were well known in prior art to inhibit Hedgehog/Smoothened (Hh/Smo) signaling specifically (see e.g. specification, page 3, lines 1-6 and the scientific publications cited therein). Cyclopamine and jervine were shown to inhibit selectively the differentiation events induced specifically by a Hedgehog protein in developing embryo to produce the previously well known cyclopia-causing and other teratogenic effects of *Veratrum* alkaloids and it was concluded that these compounds specifically inhibit Hh signaling (see e.g. *Incardona JP et al, Development* 1998; 125:3553-3562, Abstract, "*... cyclopamine-inducecd teratogenesis is due to a… direct antagonism of Shh signal transduction"; Cooper MK et al, Science* 1998;280:1603-1607, Abstract, "*... these compounds specifically block the Sonic hedgehog (Shh) signaling pathway").* Thus, non-cyclopamine molecules (e.g. jervine) that specifically inhibit Hh signaling were well known in prior art and the specification of application mentions this fact (for another example of such a molecule, KAAD-cyclopamine, see the scientific publication cited on page 3, lines 11-13 of specification). Numerous non-cyclopamine molecules without a cyclopamine core were also described in prior art to specifically inhibit Hh signaling. For example, the anti-Shh antibody H4 used in the scientific publication cited on page 3, lines 5-6 of specification *(Incardona JP et al, Development* 1998;125:3553-3562; see page 3554, right column, last paragraph) is an antibody that recognizes the biologically active signaling Shh molecule and inhibits Hh signaling specifically (see e.g. the *Ericson J et al, Cell* 1996;87:661-673 article co-authored by an author of the *Incardona JP et al* article; see page 662, left column, paragraphs 2-3).

Other neutralizing antibody molecules, e.g. the monoclonal antibodies 5E1 and AP.G6, were also described in prior art to inhibit Hh signaling specifically, both *in vitro* and ***in** vivo* (see e.g. *Ericson J et al, Cell* 1996;87:661-673; *Wang LC et al, Journal of Investigative Dermatology* 2000; 114:901-908 and the *Goodrich LV et al, Neuron* 1998;21:1243-1257 article cited on page 3, lines 4-7 of PCT/TRO2/00017 incorporated into this application). Still other categories of non-cyclopamine molecules exerting a specific inhibition of Hh signaling were also described in prior art. For example, several variants of Shh-N were identified and shown to specifically inhibit Hh signaling in assays used for demonstrating inhibition of said signaling by cyclopamine and by neutralizing antibodies (the assays included the induction of Gli1 expression by normal Shh-N and the induction of differentiation; see e.g. *Williams KP et al, Journal of Cell Science* 1999;l12:4405-4414). Another example of a non-cyclopamine molecule without a cyclopamine core described in prior art to specifically inhibit Hh signaling is HIP (Hedgehog-Interacting-Protein, *"a direct and highly specific antagonist"* of Hh signaling; see *Chuang PT et al, Nature* 1999;397:617-621; *Treier M et al. Development* 2001;128:377-386).

In conclusion, numerous naturally occurring and synthetic non-cyclopamine molecules with and without a cyclopamine core were well known in prior art to be suitable for specifically inhibiting Hh/Smo signaling. Specification of application cites several examples of prior art publications describing such uses of non-cyclopamine molecules. The specification describes also that Hh/Smo signaling is used for inhibition of differentiation and for inhibition of apoptosis of tumor cells in Basal Cell Carcinomas (BCC) as well as in non-BCC tumors and presents examples (see e.g. page 3, lines 24-28; page 4, lines 12-17; page 15, lines 19-24; page 16, line 22 to page 17, line 11; page 19, lines 6-10; page 19, lines 27-29). It is taught in aforementioned passages and elsewhere in specification that the described and exemplified method of treatment can be used on all such tumors to cause selective and efficient differentiation and apoptosis of tumor cells to obtain decrease of size or disappearance of tumor. It is also specifically mentioned that molecules can be synthesized so as to possess the disclosed biological effects of cyclopamine (see e.g. page 10, lines 8-10; page 10, lines 22-26). Thus, it is clear to a person skilled in the art that a compound that can specifically inhibit Hh/Smo signaling and that is pharmaceutically acceptable is suitable for use in the described method of treatment. Methods for assaying Hh/Smo signaling were common knowledge in prior art and several examples of these are described in the publications cited in specification. Methods of synthesis of large libraries of related molecules (e.g. combinatorial chemistry methods) were also known and synthesis of several specific inhibitors of Hh/Smo signaling were described in prior art. Thus, after reading the specification, a person of ordinary skill in the art could readily recognize the identity of a particular non-cyclopamine molecule suitable for use in the described method of treatment and he/she could easily obtain further such molecules. Thus, the specification supports claim 39 and said claim fulfils the written description and enablement requirements.

Claim 40 is directed to a method of inducing differentiation of the tumor cells that use Hh/Smo signaling for inhibition of differentiation. The specification of the application describes that a specific inhibitor of Hh/Smo signaling can be used to induce differentiation of said cells and, by adjusting the amount and duration of application of such an inhibitor, one can obtain differentiated cells that have not apoptosed (see e.g. page 5, line 21 to page 6, line 5; page 8, lines 21 -27; page 13, line 12 to page 14, line 2; page 18, line 4 to page 19, line 2).

New claims 39 and 40 are seen to be patentable over the prior art at least for the reasons given above and articulated earlier for claims 33 and 2.

Respectfully submitted,
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Attachments:
Incardona JP et al, Development 1998; 125:3553-3562
Cooper MK et al, Science 1998;280:1603-1607
Ericson J et al, Cell 1996;87:661-673
Wang LC et al, Journal of Investigative Dermatology 2000; 114:901-908
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